



US005480999A

**United States Patent**

[19]

**Chabrier De Lassauniere et al.**[11] **Patent Number:** **5,480,999**[45] **Date of Patent:** **Jan. 2, 1996**

[54] **DUAL INHIBITORS OF NO SYNTHASE AND CYCLOOXYGENASE, THERAPEUTICAL COMPOSITIONS CONTAINING THEM**

[75] Inventors: **Pierre-Etienne Chabrier De Lassauniere**, Paris; **Pierre Braquet**, Garches; **Colette Broquet**, Boulogne; **Serge Auvin**, Michel-Sur-Orge, all of France

[73] Assignee: **Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S.)**, France

[21] Appl. No.: **995,792**

[22] Filed: **Dec. 23, 1992**

[30] **Foreign Application Priority Data**

Jan. 4, 1992 [GB] United Kingdom ..... 92 00114

[51] **Int. Cl.<sup>6</sup>** ..... **C07D 209/28**; C07D 207/33; C07C 229/26; C07C 2/251/04; A61K 31/405; A61K 31/155

[52] **U.S. Cl.** ..... **548/500**; 560/169; 562/440; 548/324.1

[58] **Field of Search** ..... 548/500, 374.1; 560/169; 562/440; 514/420, 532, 423, 570

[56] **References Cited**

**U.S. PATENT DOCUMENTS**

5,081,148 1/1992 Braquet et al. ..... 514/162

**FOREIGN PATENT DOCUMENTS**

140492	5/1985	European Pat. Off. .
424028	4/1991	European Pat. Off. .
6838M	5/1969	France .
2262529	9/1975	France .
2478092	9/1981	France .
2240041	7/1991	United Kingdom .
9104023	4/1991	WIPO .
9104024	4/1991	WIPO .

**OTHER PUBLICATIONS**

Patent Abstracts of Japan, vol. 61, No. 65, Nov. 10, 1980 (Tokyo Yakuhin Kogyo KK).

Olken et al., "Inactivation of Macrophage Nitric Oxide Synthase Activity by N<sup>G</sup>-Methyl-L-Arginine", Biochem. Biophys. Res. Commun. vol. 177, No. 2, 1991, pp. 828-833. Flower et al., "Analgesic-Antipyretics and Anti-Inflammatory Agents", Pharmacological Basis Of Therapeutics, chapter 29, Goodman and Gilman 1985, pp. 674-715.

Auguet et al., "Endothelium independent protective effect of N<sup>G</sup>-monomethyl-L-arginine on endotoxin-induced alterations of vascular reactivity", Life Sciences, 1991, 48, 189-193.

Auguet et al., "Induction of nitric oxide synthase by lipoteichoic acid from *Staphylococcus aureus* in vascular smooth muscle cells" FEBS vol. 297, Feb. 1992, pp. 183-185.

Chabrier et al., "Regulation of a trial natriuretic factor receptors by Angiotensin II in rat vascular smooth muscle cells", J. Biol. Chem. 1988, 263, 13199-13202.

W. Armstrong, "Recent trends in research and treatment of stroke" SCRIP, PJB Publications, 1990, pp. 84-87.

Moncada et al., "Nitric Oxide: Physiology, Pathophysiology and Pharmacology", Pharmacological Reviews 43, 2, 109-142 (1991).

Auguet et al., "Comparative effects of endothelin and phorbol 12-13 dibutyrate in rat aorta", Life Sciences, 1989, 45, 2051-2059.

Cazenave et al., "L'agregation plaquettaires: outil d'investigation clinique et d'etude pharmacologique-Methodologie", Ann. Biol. Chem. 1983, 41, 167-179.

Green et al., "Analysis of Nitrate, Nitrite and [<sup>15</sup>N] Nitrate in Biological Fluids", Analytical Biochemistry, 126 (1982), 131-138.

Duverger et al., "Systemic administration of a PAF-antagonist, BN 50739, protects against cerebral ischemia", Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1990, 409-413.

*Primary Examiner*—David B. Springer  
*Attorney, Agent, or Firm*—Lucas & Just

[57] **ABSTRACT**

The invention relates to compounds of the general formula